from the filtrate under reduced pressure. The residue was distilled through a short-path apparatus, bp 100 °C (0.004 kPa; 0.03 mmHg), to yield 0.75 g (63%) of an oil. This was converted to its HCl salt with ethereal HCl and was recrystallized (see Table I).

Method F. Reductive Alkylation of a Secondary Amine with Formaldehyde and Pd/C. 1-(3,4-Dimethoxyphenyl)-2-(*N*-methyl-*N*-isopropylamino)propane Hydrochloride (12). The free base of 11 (1.47 g, 0.0062 mol) and 3 mL of 37% aqueous formaldehyde were hydrogenated in the presence of 0.2 g of 10% Pd/C in 80 mL of anhydrous EtOH at an initial pressure of 248 kPa (36 psig). After 1 h, the calculated amount of H_2 was absorbed; the reduction mixture was filtered and volatiles were removed from the filtrate under reduced pressure. The oily residue was treated with excess 5% KOH and this mixture was extracted with Et_2O. The volatiles were removed from this extract; the oily residue was taken up in 10% HCl and this solution was extracted with Et_2O, which was discarded. The aqueous phase was treated with excess KOH and was extracted with Et_2O. The extract was dried ($MgSO_4$) and the Et_2O was removed under reduced pressure to leave an oil: bp 101 °C (0.004 kPa; 0.03 mmHg); yield 1.40 g (90%); NMR ($CDCl_3$) δ 2.25 (s, 3 H, N-CH_3). This material was converted to its HCl salt with ethereal HCl, and the salt was recrystallized (see Table I).

Ether Cleavage Reactions. The amine or its HCl salt (0.001 mol) was heated under N_2 with 6 mL of 48% HBr at 110–120 °C for 3 h. Volatiles were removed under reduced pressure, and the residue was recrystallized (see Table I).

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Conformational Analogues of Dopamine. Synthesis and Pharmacological Activity of (*E*)- and (*Z*)-2-(3,4-Dihydroxyphenyl)cyclopropylamine Hydrochlorides

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(*E*)- and (*Z*)-(±)-2-(3,4-dihydroxyphenyl)cyclopropylamine hydrochlorides were synthesized as part of a program to assess the importance of conformational isomerism with respect to the various peripheral biological actions of dopamine. Although neither of the compounds possessed dopaminergic activity in the canine renal blood-flow model, both agents were weak α-adrenergic agonists and exhibited cardiostimulatory properties similar to dopamine. The *E* isomer was approximately 5 times more potent than the *Z* isomer in its α-adrenergic activity and approximately 15 times as potent in its cardiac effects. Possible reasons for the lack of renal dopaminergic activity exhibited by the *E* isomer are presented.

Dopamine is known to interact with a variety of peripheral receptors. In addition to its vasodilator activity in renal and mesenteric vascular beds, dopamine interacts with β_1- and α-adrenergic receptors[1] and induces release of norepinephrine from sympathetic nerves in the heart.[2] As part of a program to design a more specific dopaminergic agent[3] and to define the importance of certain molecular conformations of dopamine that might be

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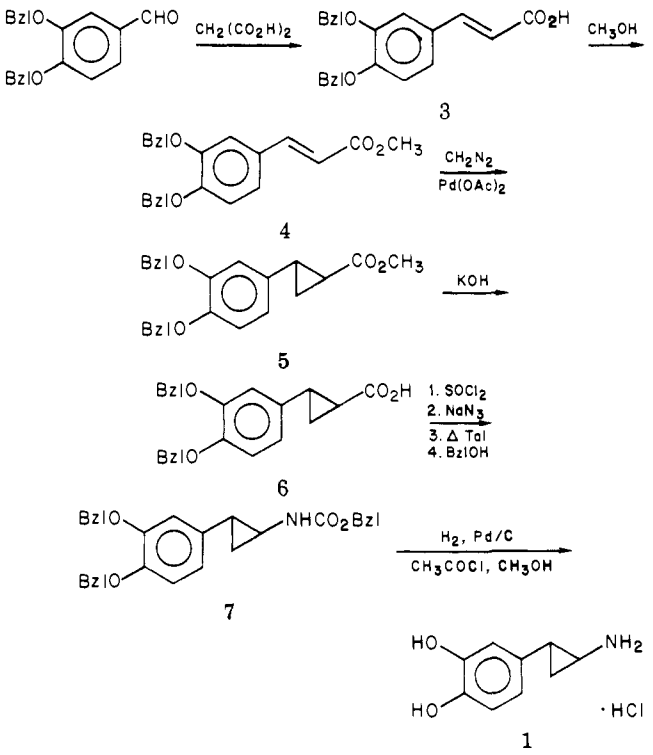
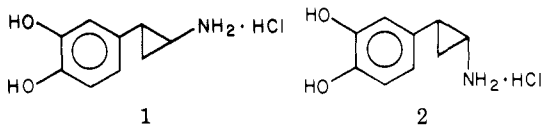
Scheme I



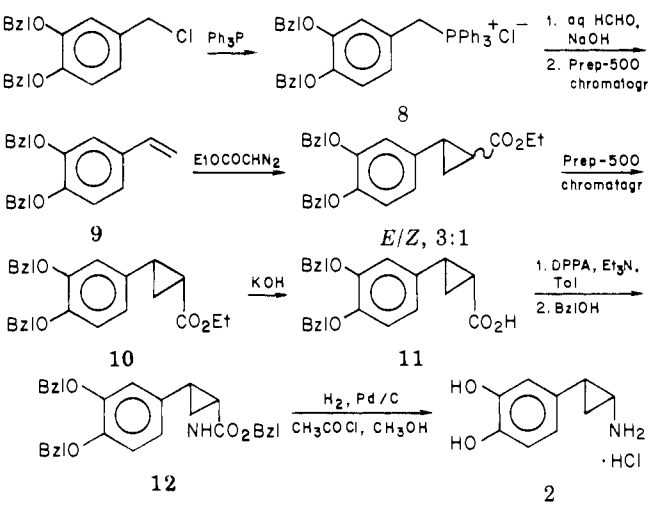
preferred for interaction with these various receptors, the semirigid dopamine analogues **1** and **2** were synthesized



as models of the extended and folded forms of dopamine, respectively. Although the close structural similarity of **1** to dopamine has been noted in the literature,[4] the synthesis of this compound has not been accomplished previously, probably owing to its facile decomposition when treated with acid. Therefore, the syntheses of **1** and **2** are described in detail.

Chemistry. Established chemistry associated with tranylcypromine provided a background[5-7] for the development of synthetic routes to **1** and **2**. It was felt that a stereoselective approach, as depicted in Scheme I, would be most convenient for the synthesis of the thermodynamically more stable *E* isomer.[8] In this regard, Knovenagel condensation of 3,4-bis(benzyloxy)benzaldehyde with malonic acid provided the substituted cinnamic acid **3** and established the desired *E* stereochemistry.[9] Acid **3** was converted to its methyl ester to enhance ethereal solubility, and cyclopropanation with retention of stereochemistry was then accomplished with ethereal diazomethane in the presence of catalytic palladium diacetate.[10] Hydrolysis of the cyclopropyl ester provided acid **6** ready for Curtius conversion to the amine. NMR spectral studies confirmed the *E* stereochemical integrity of **6**, since the diagnostic[11] cyclopropane resonances were identical with those for (*E*)-2-phenylcyclopropanecarboxylic acid.[12] Quantitative conversion of **6** to its acid chloride occurred readily at room temperature when the acid was dissolved in an equal mixture of toluene–thionyl chloride. This procedure is considerably gentler than those previously reported[13] for related systems where cis to trans isomerization also occurred. The acid chloride was converted to its acyl azide employing a wet sodium azide method,[14]

Scheme II



and the acyl azide rearranged to the isocyanate in refluxing toluene. An attempted conversion of the isocyanate to an amine employing strong acid[5] led to severe decomposition. This was surprising in view of the success of model reactions with 3,4-bis(benzyloxy)phenethylamine and with 2-phenylcyclopropane isocyanate. However, while each of the model systems is stable, it is suspected that the combination of a cyclopropyl ring and a para-oxygenated aryl system is labile due to a "push–pull" mechanism, where electron donation from the para-oxygen substituent contributes to the acid-promoted cyclopropane ring cleavage. Interestingly, such an electron flow from the acyl system is opposite in its direction when compared to related cyclopropylamines reported to suffer ring opening under basic[15,16] and neutral[16] conditions via electron flow from the amino free-electron pair. However, under acidic conditions amine protonation should preclude the latter pathway. Because of this decomposition, realization of the amine function was achieved by first isolating benzyl carbamate **7** and subjecting this intermediate to catalytic hydrogenolysis.[14] This process also removed the phenolic-hydroxyl protecting groups and provided **1** directly. NMR spectral studies substantiated the stereochemical integrity of **1**, since the cyclopropane resonances were identical with those for tranylcypromine hydrochloride.

The synthetic approach to the *Z* isomer is depicted in Scheme II. Reaction of 3,4-bis(benzyloxy)benzyl chloride with triphenylphosphine provided the Wittig reagent **8** in quantitative yield. The acidic benzylic proton of this reagent is conveniently removed with sodium hydroxide in situ, and subsequent reaction with aqueous formaldehyde generates the substituted styrene **9** in high yield.[17] Triphenylphosphine oxide was removed by silica gel chromatography of a hexane extract from the reaction mixture. Repetitive treatment of **9** with ethyl diazoacetate in refluxing xylene[5,18] produced a mixture of the *E* and *Z* isomers in low yield. As expected,[18] LC examination of the product mixture indicated an approximate 3 to 1 ratio of *E* to *Z* isomers. Large-scale quantities of the esters were separated by repetitive Prep-500 chromatography. Hydrolysis of these esters to the corresponding acids **6** and **11**, followed by NMR spectral studies,[11,12] provided unequivocal assignment of stereochemistry to this point. The Curtius sequence to the benzyl carbamate **12** employing diphenylphosphoryl azide[19,20] was found to occur without epimerization, and this expeditious procedure was substituted for the more tedious mixed-anhydride method[21,22] required in earlier syntheses of related cis systems.[13] As before, catalytic hydrogenolysis of the benzyl carbamate

Table I. Pharmacological Data for 1 and 2

compd	dopaminerg renal vasodilat: ED_{50}, $\times 10^{-8}$ mol	α-adrenerg act.: EC_{50}, $\times 10^{-7}$ mol	cardiac stimulatory properties: potency,[a] $\times 10^{-8}$ mol/kg iv	cardiac stimulatory properties: inotrop selectiv[b] (BPM)[c]
dopamine hydrochloride	1.95 (5)[d]	102[33]	4.8 ± 0.6[f] (5)[d]	5 ± 5[f]
1	inact[e]	94 ± 12[f] (4)[d]	19.5 ± 1.3[f] (5)[d]	−2 ± 3[f]
2	inact[e]	457 ± 53[f] (4)[d]	312.3 (2)[d]	32
phenylephrine hydrochloride		2.3 ± 0.2[f] (8)[d]		
isoproterenol hydrochloride			0.014 ± 0.001[f] (38)[d]	16 ± 1[f]

[a] Dose producing a 50% increase in contractile force. [b] Change in heart rate associated with a 50% increase in contractile force. [c] While selectivity was maintained for dopamine at a 100% increase in contractile force ($\Delta HR = 12 \pm 5$), compound 1 was less selective ($\Delta HR = 27 \pm 4$, $N = 19$)[32] and comparable to that of isoproterenol ($\Delta HR = 38 \pm 2$) at this level of contractile force. Compound 2 did not produce a 100% increase in contractile force at 3.97×10^{-6} mol/kg where ΔHR was 46. [d] Number of experiments. [e] No dopaminergic effect observed at doses up to 4.96×10^{-6} mol intrarterially. [f] Mean ± standard error.

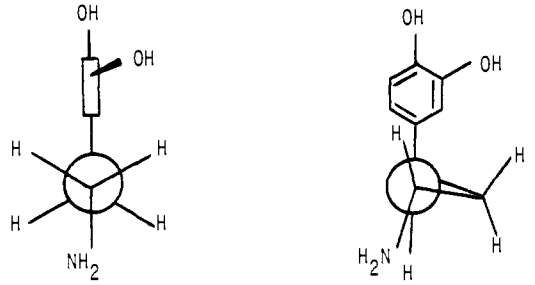


Figure 1. Newman projections of dopamine in its extended planar conformation[29] and of 1.

provided 2 directly. A method for converting these acids to their amines, without removing the catechol-protecting groups, has also been developed.[23]

Pharmacology. Table I summarizes the biological data obtained for 1 and 2. As previously reported,[3] the extended analogue 1 did not show dopaminergic agonist or antagonist activity in the canine renal blood-flow model.[24] Further examination in striatal adenylate cyclase systems[25] has also shown 1 to be essentially inactive as a dopaminergic agonist or antagonist; only weak, partial agonist activity was observed at concentrations as high as 1000 μM. Similarly, the binding capacity of 1 for central dopaminergic receptors appears to be approximately one-fifth that of dopamine when determined by the displacement of [^{3}H]spiperone from receptors in the calf caudate.[26] Finally, 1 has been found to be without effect at the presynaptic inhibitory dopaminergic receptor of the cardioaccelerator nerve.[27] This general lack of dopaminergic activity is surprising, since 1 simulates rather closely the extended conformation of dopamine which is thought[3,4] to be the preferred molecular arrangement for interaction with dopaminergic receptors (Figure 1). However, the extra methylene unit present in 1 introduces an additional steric parameter, and, although the cyclopropyl system was utilized to minimize this effect, its contribution may be similar to that found in α-methyldopamine, which is also inactive as a dopaminergic agonist. Since 1 is inactive both as an agonist and as an antagonist in the renal blood-flow model, affinity for the dopamine receptors associated with this system appears to be lacking in this agent. In this regard, the effect of the additional steric parameter could involve a negative interaction with certain topographical features of the dopamine receptor which would preclude effective receptor binding. Alternatively, its effect may simply influence the preferred conformation of these molecules, such that the plane of the aryl system and the plane of the ethylamine system are perpendicular, as illustrated in Figure 1. Since an overall planar arrangement of these groups is thought to be preferred by the dopamine receptor,[28,29] this effect could also lead to inactivity. Finally, since the electronic character of the cyclopropyl system is significantly different from that of an ethyl group, an electronic effect could also be responsible for the poor affinity exhibited by 1. Because there are noted[30] differences between various dopamine receptor populations, the proposed steric or electronic effects may apply only to those receptors associated with the renal vasculature. As expected, the folded analogue 2 was also found to be inactive in the renal blood-flow model.

The pressor activity observed during initial dopaminergic screening of 1 and 2 suggested that these agents possessed weak α-adrenergic agonist activity. This activity was examined in rabbit aortic strips[31] employing phenylephrine as a standard α agonist. The potency ranking for these agents was found to be phenylephrine > 1 > 2, with approximate potency ratios of 1:0.025:0.005, respectively. All the compounds were full agonists whose dose–response curves had similar slopes which were shifted in parallel fashion to the right after preincubation with phentolamine. These data confirm the weak α-agonist component in the pharmacological profiles of 1 and 2. Furthermore, potency comparisons between dopamine, 1, and 2 (Table I) suggest that an extended relationship between the aryl system and the amine function may also be a preferred conformational arrangement for interaction with α receptors.

The cardiac stimulant properties of 1 and 2 were determined and compared to that of isoproterenol in dogs instrumented for measurement of blood pressure, heart rate, and cardiac contractile force.[32] Like dopamine, their cardiac effects are to a large extent mediated by the indirect release of norepinephrine, since their action was diminished by pretreatment with either reserpine or desmethylimipramine. The inotropic potency ranking for these agents is isoproterenol > 1 > 2, with potency ratios of 1:0.001:0.00006, respectively. Compound 1 was the most selective, as estimated by the increase in heart rate associated with a 50% increase in contractile force. Isoproterenol and 2 were approximately equivalent and considerably less selective than 1. A further characterization of the cardiac effects and mechanisms of action for dopamine and 1 is published elsewhere.[32]

Experimental Section

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. IR spectra were obtained with a Perkin-Elmer 283 spectrophotometer either as thin films from reaction media, neat thin films, or as KBr disks. NMR spectra were recorded on a Varian Associates T-60A spectrometer. Column chromatography separations were performed on a Waters

Associates Prep-500 system at a flow rate of 250 mL/min. Mass spectra were obtained from the Analytical Services Laboratory at Northwestern University, employing a Hewlett-Packard 5985 quadrapole instrument. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

3,4-Bis(benzyloxy)cinnamic Acid (3). A mixture of 57.2 g (0.180 mol) of 3,4-bis(benzyloxy)benzaldehyde, 39 g (0.38 mol) of malonic acid, 75 mL of pyridine, and 2 mL of piperidine was heated to reflux for 2 h and then poured into 500 mL of ice–water having 100 mL of concentrated HCl. The resulting precipitate was recrystallized from 1 L of glacial acetic acid to provide 58 g (90%) of white crystals: mp 203–204 °C (lit.[34] 206–208 °C; lit.[35] 202 °C); NMR (Me_2SO-d_6) δ 6.5 (d, J = 16 Hz, 1 H, trans-olefinic =CH-). Anal. ($C_{23}H_{20}O_4$) C, H.

Methyl 3,4-Bis(benzyloxy)cinnamate (4). A suspension of 44 g (0.12 mol) of acid **3** in 750 mL of anhydrous methanol containing 25 drops of concentrated H_2SO_4 was heated to reflux in a Soxhlet extractor charged with 250 g of activated 3Å molecular sieves (1/16 pellets) for 60 h. The resulting solution was basified with 250 mL of saturated aqueous $NaHCO_3$ and cooled to provide a white precipitate, which was recrystallized from methanol: yield 44 g (95%); mp 86–87 °C; NMR ($CDCl_3$) δ 3.8 (s, 3 H, $-CO_2CH_3$). Anal. ($C_{24}H_{22}O_4$) C, H.

Methyl (*E*)-2-[3,4-Bis(benzyloxy)phenyl]cyclopropanecarboxylate (5). Diazomethane was generated slowly by adding dropwise 21.5 g (0.1 mol) of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide in 200 mL of ether to a mixture of 5 g of potassium hydroxide in 8 mL of water and 25 mL of 95% ethanol which was being warmed at 65 °C. The ethereal diazomethane (0.07 mol) distillate was delivered directly into a reaction flask containing 10 g (0.03 mol) of ester **4** and 50 mg of palladium diacetate in 300 mL of ether at 0–2 °C. After the addition, the mixture was stirred for 12 h until gradually attaining room temperature, after which it was filtered and evaporated to an oil. The oil gradually solidified at room temperature to provide 10 g (97%) of white solid: mp 49–50 °C; NMR ($CDCl_3$) δ 3.7 (s, 3 H, $-CO_2CH_3$). Anal. ($C_{25}H_{24}O_4$) C, H.

(*E*)-2-[3,4-Bis(benzyloxy)phenyl]cyclopropanecarboxylic Acid (6). A solution of 10 g (0.03 mol) of ester **5** in 100 mL of methanol containing 3.2 g (0.05 mol) of 86% KOH in 25 mL of water was heated to reflux for 3 h. The reaction medium was poured into 100 mL of 20% aqueous HCl, and the resulting precipitate was collected, washed with water until neutral to litmus (2 × 100 mL), and recrystallized from methanol to provide 7.5 g (76%) of white crystals: mp 114–115 °C; NMR ($CDCl_3$) δ 11.65 (br s, 1 H, $-CO_2H$ disappears upon addition of CD_3OD). Anal. ($C_{24}H_{22}O_4$) C, H, O.

Benzyl (*E*)-2-[3,4-Bis(benzyloxy)phenyl]cyclopropylcarbamate (7). A solution of 3.0 g (0.01 mol) of acid **6** in 15 mL of toluene and 15 mL of thionyl chloride was stirred at room temperature for 4 h. The reaction medium was then evaporated under reduced pressure, leaving the acid chloride as an oil: IR ν_{max} 1775 cm^{-1}. The oil was taken up in 30 mL of acetone, cooled to 0–2 °C, and treated dropwise with 3.0 g (0.05 mol) of sodium azide in 15 mL of water. After the addition, the mixture was stirred for 1 h until gradually attaining room temperature, then 25 mL of water was added, and the medium was extracted with toluene (2 × 70 mL). The combined extracts were dried over Na_2SO_4 and evaporated, leaving the acyl azide as an oil. The oil was taken up in toluene and warmed at 90 °C until bubbling ceased (1–4 h) and IR indicated the absence of the 2140- and 1705-cm^{-1} absorptions. Benzyl alcohol (0.90 mL, 0.01 mol) was then added, and warming at 90 °C continued (12–24 h) until IR indicated the absence of the 2280-cm^{-1} absorption. Evaporation under reduced pressure yielded an oil which gradually solidified at room temperature. This crude product was recrystallized from methanol to provide 3.0 g (80%) of white crystals, mp 85–87 °C. Anal. ($C_{31}H_{29}NO_4$) C, H, N.

(±)-(*E*)-2-(3,4-Dihydroxyphenyl)cyclopropylamine Hydrochloride (1). A solution of 1.30 g (0.003 mol) of carbamate **7** and 0.470 g (0.006 mol) of acetyl chloride in 200 mL of methanol with 250 mg of 10% palladium/carbon was hydrogenated at 20 psi for 20 min. The reaction medium was then filtered, reduced in volume to 10 mL, and treated with anhydrous ether (75 mL) until faintly turbid. Crystallization and subsequent recrystallization in a similar fashion occurred at room temperature and provided 0.30 g (56%) of yellow needles: mp 186–187 °C; EIMS M^+ 165 (100%) with an appropriate M – 2 peak comparable to that found with dopamine.[36] Anal. ($C_9H_{12}NO_2Cl$) C, H, N.

[3,4-Bis(benzyloxy)benzyl]triphenylphosphonium Chloride (8). A mixture of 250 g (0.738 mol) of 3,4-bis(benzyloxy)benzyl chloride and 194 g (0.738 mol) of triphenylphosphine in 2.5 L of chloroform was heated to reflux for 10 h. The solution was then concentrated (1 L), and 5 L of anhydrous ether was added to initially produce the product as an oil, which solidified upon standing and was subsequently ground to 434 g (98%) of white powder, mp 218–220 °C. This reagent was employed without additional purification.

3,4-Bis(benzyloxy)styrene (9). To a mixture of 48 g (0.08 mol) of Wittig reagent **8** in 300 mL of 40% aqueous formaldehyde at room temperature was added dropwise 45 mL of 50% aqueous sodium hydroxide. The mixture was stirred for 1 h and then extracted with ether (2 × 200 mL). The ethereal extract was dried over $MgSO_4$ and evaporated to provide a mixture of the substituted styrene and phosphine oxide as a white solid in quantitative yield. This solid was extracted with hexane (5 × 100 mL), and the combined extracts, after concentrating, were chromatographed on a silica gel column. The desired styrene was eluted using ethyl acetate as the mobile phase. Evaporation of solvent provided a white solid, which was recrystallized from ethyl acetate to provide 19 g (74%) of the desired styrene, mp 68–69 °C. Anal. ($C_{22}H_{20}O_2$) C, H.

Ethyl (*Z*)-2-[3,4-Bis(benzyloxy)phenyl]cyclopropanecarboxylate (10). A mixture of 25.0 g (0.079 mol) of styrene **9** and 9.00 mL (0.086 mol) of ethyl diazoacetate in 100 mL of xylene was heated to reflux for 24 h. A second 9.0 mL charge of ethyl diazoacetate was then added, and heating was continued for another 24 h. This procedure was repeated a third time. After the third 24-h period, the solution was concentrated to 50 mL and chromatographed on a silica gel column employing hexane–ethyl acetate (9:1) as the mobile phase. The fractions corresponding to an approximate 3:1 *E*/*Z* mixture of the desired cyclopropyl esters were combined, concentrated, and chromatographed again, employing hexane–ethyl acetate (15:1) as the mobile phase. For each injection, the first peak eluted, representing the *E* isomer, was separately collected from the second peak, which represented the *Z* isomer. The troughs between the peaks were collected separately and, after combining, rechromatographed in a similar fashion. Evaporation of the solvent from fractions corresponding to the *E* isomer provided 10 g (41%) of white solid, while evaporation of fractions corresponding to the *Z* isomer provided 3.0 g (37%) of a clear oil, which was used directly in the next reaction: NMR for *E* isomer ($CDCl_3$) δ 4.1 (q, J = 7 Hz, 2 H, $-CH_2CH_3$), 1.1 (t, J = 7 Hz, 3 H, $-CH_2CH_3$); NMR for *Z* isomer δ 3.7 (q, J = 7 Hz, 2 H, $-CH_2CH_3$), 0.9 (t, J = 7 Hz, 3 H, $-CH_2CH_3$).

(*Z*)-2-[3,4-Bis(benzyloxy)phenyl]cyclopropanecarboxylic Acid (11). Ester **10**, 2.50 g (0.006 mol), in 25 mL of ethanol was hydrolyzed according to the procedure described for **6** and provided 2.0 g (86%) of white crystals: mp 123–124 °C; NMR ($CDCl_3$) δ 6.6 (br s, 1 H, $-CO_2H$, disappears upon addition of CD_3OD). Anal. ($C_{24}H_{22}O_4$) C, H.

Benzyl (*Z*)-2-[3,4-Bis(benzyloxy)phenyl]cyclopropylcarbamate (12). A mixture of 1.63 g (0.004 mol) of acid **11**, 1.18 g (0.004 mol) of diphenylphosphoryl azide, and 0.60 mL (0.004 mol) of triethylamine in 75 mL of toluene was heated to reflux for 2 h. Benzyl alcohol (0.44 mL, 0.004 mol) was then added and refluxing continued for 48 h. The reaction medium was then partitioned with 25 mL of 5% aqueous HCl, 25 mL of water, 25 mL of aqueous $NaHCO_3$, and 25 mL of water. The toluene phase was dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The resulting solid was recrystallized from ethanol to provide 1.4 g (67%) of white crystals, mp 126–127 °C. Anal. ($C_{31}H_{29}NO_4$) C, H, N.

(±)-(*Z*)-2-(3,4-Dihydroxyphenyl)cyclopropylamine Hydrochloride (2). A solution of 2.97 g (0.006 mol) of carbamate **12** and 2.0 mL (0.028 mol) acetyl chloride in 1.7 L of methanol with 2 g of 10% palladium/carbon was hydrogenated at 40 psi for 20 min. The reaction medium was then filtered, reduced in volume to 50 mL, and treated with 1 L of ethyl acetate until faintly turbid. Crystallization was accomplished slowly at room temperature and provided 0.58 g (46%) of yellow rosettes: mp 206–207

°C; EIMS M^+ 165 (100%) with an appropriate M − 2 peak comparable to that found with dopamine.[36] Anal. ($C_9H_{12}NO_2Cl$) C, H, N.

Renal Dopaminergic Activity. The dog renal blood-flow model was prepared essentially as described by Goldberg et al.[24] Male mongrel dogs (10–15 kg) were anesthetized by iv injection of pentobarbital, 30 mg/kg. Dogs were intubated and ventilated with positive pressure, and the left femoral vein was cannulated for supplemental anesthetic and saline infusion. The right renal artery was exposed through a flank incision and an appropriately sized electromagnetic flow probe was placed around the artery. A 27-gauge needle bent into an acute angle was inserted into the artery distal to the probe and connected to saline-filled syringes on an infusion pump. Dopamine hydrochloride and compounds **1** and **2** were injected directly into the renal artery via the needle, and dose–response relationships were obtained for each of the compounds. This procedure was repeated after establishing α blockade, which was obtained by infusing phenoxybenzamine hydrochloride (POB), 5 mg/kg, into the renal artery over a period of about 25 min; approximately 200 mL of 0.9% saline was concommitantly infused into the femoral vein to reduce the fall in blood pressure seen with POB. Norepinephrine, 10 μg, injected into the renal artery, was used to test the adequacy of α blockade.

α-Adrenergic Activity. Aortic strips from male rabbits (2–3 kg) were prepared essentially as described by Besse and Furchgott.[31] Each rabbit was stunned and exsanguinated. The thoracic aortas were removed and placed in warm (37 °C) oxygenated (0.5% O_2–5% CO_2) Krebs medium (composition, mM: NaCl, 118.39; KCl, 4.70; $MgSO_4 \cdot 7H_2O$, 1.18; KH_2PO_4, 1.18; glucose, 11.66; $CaCl_2$, 2.52; $NaHCO_3$, 25.00; Na_2EDTA, 0.03). Tissues trimmed of fat and connective tissue were cut into spiral strips approximately 3–4-mm wide and 3–4-cm long and placed in 30-mL tissue baths for measurement of isometric contraction. Resting tension was set at 4 g. Tissues were washed periodically, and tension was readjusted during the initial 1-h equilibration period and as necessary before each concentration–response curve. Cumulative concentration–response curves were run for *l*-phenylephrine hydrochloride and for **1** and **2**. Studies were also performed in the presence of phentolamine hydrochloride. Results at each concentration were calculated as a percent of maximal response to phenylephrine; EC_{50} values were obtained by linear regression analysis in each experiment and the results averaged.

Cardiac Activity. Compounds **1** and **2** were tested for cardiac stimulant activity in dogs instrumented for measurement of contractile force, diastolic arterial blood pressure, and heart rate.[32] The left femoral artery was cannulated for measurement of arterial blood pressure. The heart rate was measured using a cardiotachometer triggered off the pulsatile arterial blood pressure signal. The animals were ventilated with positive pressure and underwent a right thoracotomy in the fifth intercostal space. A precalibrated Walton–Brodie strain gauge was sutured to the right ventricle to measure cardiac contractile force. Testing began with a dose of 0.78 μg/kg bolus (drug dissolved in saline containing 0.5 mg/mL sodium bisulfite) and dosing was continued in twofold steps until a 100% increase in contractile force was obtained or until a maximum dose of 400 μg/kg was administered. The heart rate associated with the 50 and 100% increase in cardiac contractile force was obtained by interpolation from log dose–response curves. Dopamine hydrochloride and isoproterenol hydrochloride were tested for comparison with the test compounds.

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